MEMORANDUM
Reclassification Petition: Clinical Consult Review

To: Orthopaedic Advisory Panel
From: Orthopaedic Devices Branch, Division of General, Restorative and Neurological Devices;
Date: April 26, 2004
Subject: Reclassification Petition: Mobile Bearing Knee Prostheses

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Summary:
This reclassification petition presents data to support the petition for reclassification of all mobile bearing unicondylar, bicondylar condylar and tricompartmental knees from Class III to Class II. This includes clinical data from IDE and outcome studies, peer reviewed journal articles and meta- analysis comparison analyses between fixed and mobile bearing systems related to adverse events and effectiveness outcomes. The sponsor believes that this information provides strong evidence of the safety and efficacy of mobile bearing knees, and that the risks associated with these devices are now adequately defined. Before a decision can be made whether reclassification from Class III (Premarket Approval Application) to Class II (Special Controls) is justified, further information and clarification is needed.

Background:
Reclassification is requested from Class III to Class II.
There are numerous mobile bearing knee designs on the market worldwide
designed to increase contact area and /or to reduce implant-to-bone interface stresses by allowing mobility of the polyethylene bearing on the tibial plate in order to potentially reduce long-term wear.

Regulatory History of the Device Class
FDA issued a Proposed Rule classifying 77 orthopedic devices on July 2, 1982 (47 FR 29052), and the Final Rule on September 4, 1987 (52 FR 33686). The Final Rule established twelve separate categories of implantable knee prostheses (21 CFR 888.3480 through 888.3590). Each of the twelve types of knee prostheses described were assigned to either Class II or Class III depending on system attributes such as fixation method, level of constraint, and degree of resurfacing (e.g., patellofemorotibial versus femoral).

None of the categories, however, describes the type of total knee replacement system that has come to be known as the mobile bearing knee.

The question of reclassification of mobile bearing knees from Class III (Premarket Approval) to Class II (Special Controls) was considered by an FDA Advisory Committee on January 13, 1998. At that time, the panel's recommendation was to retain the Class III designation for all tricompartmental and unicompartmental mobile bearing knees with the exception of recommending reclassification of tricompartmental mobile bearing knees
that are cemented and have a rotating/translating base. The panel also recommended post-market surveillance for those mobile bearing knees reclassified to Class II. The FDA subsequently chose to recommend submission of a new reclassification petition for the entire class of mobile bearing knees, rather than reclassify specific subcategories.

Device History
The first mobile bearing knee designs were introduced in the late 1970's. The Oxford Unicondylar knee (Biomet, Inc., Warsaw, IN) was the first to utilize a mobile bearing to reduce contact stress while also reducing implant-to-bone interface stress. Since those early implants, several generations of mobile bearing knees have followed, and today there are nearly 50 unicondylar and bi-condylar implant designs with either platform-style or meniscal bearing design of the polyethylene articulating surface on the international market. There are numerous variations in the directional

mobility of the polyethylene, type of constraint of the polyethylene, and treatment of the PCL. The first mobile bearing knee to be approved by the FDA for sale in the U.S. was the Low Contact Stress (LCS) Rotating Platform Knee (J&J DePuy, Warsaw, IN). PMA approval for this knee was received in 1985, and since then five other mobile bearing knees have been approved in the U.S.

Reclassification of several types of knees from Class III to Class II was considered by an FDA Advisory Panel on January 13, 1998 ("Petition for Reclassification, Patello-Femoral-Tibial Metal/Polymer/Metal/Polymer/Metal Biologically Fixed Prosthesis, submitted by the Orthopedic Surgical Manufacturers Association, July 25, 1997). Mobile bearing knees were included in that petition. At that time, the Panel believed there was insufficient evidence to provide reasonable assurance of safety and efficacy for the entire class of mobile bearing knees. They recommended reclassification only of tricompartmental mobile bearing knees that are cemented and have a rotating/translating base. However, they recommended the retention of Class III designation for all other tricompartmental and unicompartmental mobile bearing knees.

At this time 6 devices are available in the US:
- Low Contact Stress (LCS) Rotating Platform
- P.F.C. Sigma Rotating Platform
- P.F.C. Sigma Stabilized Rotating Platform
- Low Contact Stress (LCS) Meniscal Bearing
- Low Contact Stress (LCS) Unicompartmental Knee
- Oxford Meniscal Unicompartmental Knee

Intended Use:

The intended use differs depending on the subtype.

The mobile bearing total knee, fixed with or without bone cement is indicated for:

- Patients with knee pain and disability due to rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis, collagen disorders and/or avascular necrosis of the femoral condyle
- Post-traumatic loss of joint configuration (particularly when there is patellofemoral erosion, dysfunction, or prior patellectomy)
- Moderate valgus, varus, or flexion deformities
- The salvage of previously failed surgical attempts if the knee can be satisfactorily balanced and stabilized at the time of surgery

The mobile bearing unicompartmental Knee, fixed with or without bone cement is indicated for:
- Patients with knee pain and disability due to osteoarthritis or traumatic arthritis
- Previous tibial condyle or plateau fractures with loss of anatomy or function
- Varus or valgus deformities
- Use with an intact Anterior Cruciate Ligament (ACL)
- Revision of previous unicompartmental arthroplasty procedures

Device Description/Principle of Operation:

This class of devices includes two subtypes: bicondylar knee joint patellofemorotibial metal/polymer mobile bearing cemented or porous coated uncemented prosthesis" and
Unicondylar knee joint femorotibial (uni-compartmental) metal/polymer mobile bearing
cemented or porous coated uncemented prosthesis"

The defining feature of a mobile bearing knee is the presence of a moving polyethylene bearing that articulates with both the femoral condyle and the tibial tray. It is theorized that mobile bearing knee designs potentially reduce polyethylene wear by their highly conforming surface that disperses contact forces over a large area. The mobility in the polyethylene bearing, which reduces implant-to-bone interface stresses, may prevent implant loosening, which has been attributed to high interface stresses in highly conforming fixed bearing knee designs.

Mobile bearing knees are available in PCL-retaining, PCL-sacrificing and PCL stabilizing designs. In general, knees with only rotating mobility utilize a PCL sacrificing or PCL-stabilizing design, while multidirectional platform knees generally are PCL-retaining.

These devices can be further categorized by the type of bearing surface (Platform, bicondylar meniscal bearing, and unicondylar meniscal bearing), type of constraint and type of fixation (cemented , porous coated uncemented).
Bearing Surface included:

- Platform: a single polyethylene bearing that rotates in the transverse plane, with or without A/P motion (rotating only or multidirectional).
- Meniscal Bearing: separate medial and lateral polyethylene bearings that slide independently in arced tracks that run anteriorly and posteriorly in the fixed, metal tibial component
- Unicondylar Meniscal Bearing: an implant in which only the medial or lateral compartment of the knee is replaced. The polyethylene may run in a track as described above, or may move freely, held in place only by its reciprocal shape and the tension of the surrounding ligaments.

Past experience and literature have shown that the use of cement has improved results and higher failure rates are associated with non cemented use. In light of this information, it should be considered whether we can include uncemented (porous coated) devices with cemented devices (i.e. do we have enough data to feel comfortable that special controls will predict safe use).

Type of Constraint (prevention of bearing dislocation)
Unconstrained designs have very low constraint forces over the entire range of normal (physiologic) displacements.
Semi-constrained designs have near physiologic constraint that rises over the range of normal displacements.
Constrained designs have constraint forces that exceed physiologic levels and rise sharply over the range of displacements

- Cone-in-cone Design: incorporates a tapered projection of the polyethylene insert that inserts into a reciprocal concavity in the tibial tray
- Tibial Tray Post: A post extending from the superior surface of the tibial tray fits into a recess on the polyethylene insert
- Longitudinal Curved Sliding Tracks: Movement of the platform or meniscus is limited by a track formed in the upper surface of the tibial tray
- Stops: elevated rim of the tibial tray that limits excessive A/P translation or rotation
- Unconstrained Bearing: designs that lack a mechanical limit to movement, but instead rely on the conformity of the polyethylene mobile bearing to the femoral condyle and the tension of the soft tissues

Characterization of the Directional Mobility of the Bearing Surfaces:
Nine knee designs were tested in a dynamic testing system in which compressive load was applied as the knee was rotated or moved in the A/P or M/L direction. Torque or shear forces were measured and plotted against displacement, thus characterizing the ability of the knee design to constrain displacement during gait. The nine designs were then characterized as "unconstrained", "semiconstrained", and "constrained". Of the nine designs evaluated, all demonstrated unconstrained motion in the rotational direction and all the mobile bearing designs demonstrated unconstrained mobility within a total of 15 degrees internal/external rotation. Relative to M/L mobility, the designs tested were evenly divided between semi-constrained and constrained mobility. Constrained and semiconstrained M/L mobility is characteristic of both mobile and fixed bearing knee designs, and does not adversely affect clinical performance. Analysis of A/P mobility revealed a wide range of constraint, with unconstrained designs prevailing. In order to achieve joint stability with the lower level of constraint, competent soft tissue, including balanced collaterals and/or the PCL are necessary.

• Congruence:
Fully congruent mobile bearing knees are those that have a high degree of conformity between the femoral condyle and the polyethylene bearing surface, over a wide range of flexion (approximately 120 degrees). accomplished by providing a constant sagittal femoral radius, limited by posterior impingement of the tibial component. A fully

congruent prostheses has a large contact area between the femoral condyle and the bearing surface, disperses contact forces, thereby theoretically resulting in reduced polyethylene wear.

Gait congruent or partially congruent mobile bearing knees have large contact areas in the first 20 degrees of flexion. The contact area decreases with flexion due to a decreasing sagittal radius. These prostheses maximize contact areas in the low end of the flexion range, while decreasing the sagittal radius to improve flexion range.
The term "functionally congruent" is used to mean that a device has a single femoral radius for up to 75 degrees of flexion.

Summary of Unpublished IDE data

	BIOMET TRAC PS Rotating Platform	**OXFORD UNICOND Phase II Meniscal Bearing**	**S&N GEN II Rotating P, Multidirectional P**	**PROFIX RP MP**	**STRYKER HO SCORPIO PS RP**	**ZIMMER MOBILE BEARING KNEES MP**	**ZIMMER** NEXTGEN **LPS FLEX RP**
Type	P, MC, Rand	P,MC	P,MC,R	P,MC,R	P,MC,R	P,MC, NR	P,MC,R
#enrolled	130 (all cemented)	125 knees(all cemented) 107 pts	109/119 cemented 94/104knees uncemented 15 hybrid	59 50 cement 9 hybrid	62	179	61cemented
1 yr	103	104/125	106 pt		41 pts @ 7 weeks; (6 mo 12pts)	145	81/123(65%)
2 yr (%)	89		3			51%	
3 yr	333						
4 yr f/u	6						
Mean F/U	2.2 yr	4.8	1 yr	9 mo	3 mo	1.5 yr	
Age Mean	65 (40-87)	62 (34-85)	64-65	64	63	65	62
KSS/HSS Good-Excellent	KSS 1 yr 77.4% 2 yr 83.7% 3 yr 85% 4 yr 100%	HSS 95.2 95 14% required walking support	89= ave KSS	KSS 92%	75% 6mo	KSS 89.7 89.3	KSS 84%
Revisions	7	16 (7?) survivor ship 94% @ 6 yrs 88% cumulative @ 6yrs	2(1yr)	0	0	3	0
Reasons	-Poly (multiple) dislocation(11) -Insert subluxation (1) -Pt dislike	-Poly dislocation(4%) -Deep infection -Lat compartmt degeneration -Aseptic loosening	-deep infection(1yr) -poly subluxation(3mo) -Fracture -Fibroarthrosis -RSD		-Wound healing probs medial epicondyle avulsion IPL disruption	-deep infection -pain -PCL insufficiency	

		:femur and tibia -poly wear -patellar complication -RA onset -Auto Accident -Patella Dislocat -improper alignment -meniscal cyst 1 pt death					
Rev Rate (sponsor)	5.4%	15.4	1.7			1.7	

*Note that in all of the studies 85-100% of patients had OA as a primary diagnosis.

International Studies

	Zimmer MOBILE BEARING KNEES			**NexGen LPS-Flex**		
# enrolled	1,254			390		
Insall Categories	A	B	C	A	B	C
1 yr	447/552 (80%)	223/256	143/213 (81%)	80/86	24/30	55/60
2 yr (%)	223/256 (87%)	117/140 .(83.6%)	74/100 (74%)	15/15	3/5 (60%)	4/4
Mean F/U	33% at 2 yrs					
KSS/HSS **Good-Excellent**	81% 85.7	87% 83.8%	67% 74%	93% 100	79 67	91 100
Revisions	8 total 0.6%			2 total		
Reasons	-Patellar complications -Fixed flexion deformity/stiffness -unspecified Complication rate 3.6%			Deep infection (3 mo) Instability (6 mo)		

Data from two international clinical outcomes studies provide robust evidence of the clinical success of mobile bearing knees in general usage. These data sets represent a variety of surgical skills among numerous surgeons, in numerous countries, from general patients not limited by inclusion/exclusion criteria. Currently, 2 year data is available from a total of 243 patients. The published data is summarized in Volume 2, Appendix 3.

Overall Summary

The sponsor provides summaries of studies grouped by mobile bearing knees types. Even within these groupings, the results are variable and very few prospective randomized controlled studies are reviewed, particularly those comparing mobile bearing knees to fixed bearing total knee arthroplasty out comes. Patient population varies as do indications (Unicondylar vs. bicondylar) Although retrospective studies are useful as they provide longer term information, the data collected retrospectively has inherent flaws due in large part to missing information and the need for interpretation. Thus this data should be reviewed with some caution. It is difficult to group all the different types of mobile bearing knees into one group as they appear to have very variable results, even within the same group. The FDA believes the mechanics and adverse events may be unique for tricompartmental (patellofemorotibial) mobile bearing knees as compared to bicompartmental (femorotibial)and therefore recommend that a separate category be proposed rather than grouping these two types of devices together.

Multidirectional platform devices

This consists of 2 prospective (none randomized) and 2 retrospective studies which discuss 4 different devices implanted in 425 patients/491 knees (includes bilateral) with a major diagnosis of osteoarthritis (>70%). Follow-up averaged 4.1 years in the range of 2-8 years with variable patient follow-up percentages(as low as 35%) . The outcomes results are variable and range from poorer results for the Accord device (Duffy) at 5 years with 16% severe pain, mean knee score 60/100 and function score 42/100 and 58% survivorship at 10 yrs., to better results for the Rotaglide (Polyzoides) with pain in less than 3% of the patients(knee scores not reported). Knee scores in the other 2 studies range from 155-188/200. Some of the patients in these reviews were excluded if they had a revision.

Multidirectional Platform Devices Meta analysis				
reference	**Duffy & Philipson**	**Kaper et. Al.**	**Morgan-Jones et. al.** prospective	**Polyzoides et. al.** retrospective
Device Name	Accord TKA	Self Aligning I		Rotaglide TKA
Knees/patients	74/61 35% f/u	172/141 OA	75/62	170 cemented
Age mean (range)	68-69	71 (47-90)	67	66
Deaths	16 pts (20 knees)	41		
Lost to f/u	6	1 @ 5 yrs		
Revisions/surg	25 (19 instability) 34%	15 (8.1%)	0	0
Complications **Infection** **Aseptic loosening** **Poly wear** **Fractures** **Stiffness** **Pain** **Dislocations** **Lysis** **Instability**	 1 8 2 3 8 19	 4 4 2 4 1 1	No dislocation, subluxation, breakage, subsidence or osteolysis 1 patella replacement	No platform dislocation No mechanical implant failures 1ptw/fracture@6 wks
NSS (mean)	60 35% good –excellent, fxn 4% good to excellent	KSS pre 81 Post -155	KSS pre 96 Post 188	95% BritishOA score good/excellent
Function score	42	ROM 0° Post 111°	ROM 2yr 133°	
Survivorship	10yr= 58%	91.7 % (poly wear =98.8%		
F/U (mean)	5 yrs, 4 mo	5.6 yrs (5-8yrs)	2.5 yrs	2-5 yrs
Comment	Poor as compared to conventional TKA 16% severe pain	Pt satisfaction = 94%		

Rotating platform Devices

This consists of 2 prospective (one randomized) and 2 retrospective studies which discuss 1 device (LCS) implanted in 744 patients/939 knees (includes bilateral) with a major diagnosis of osteoarthritis (>70%). Follow-up averaged 1-12 years with variable patient follow-up percentages(as low as 55%) . The outcomes results are variable. Knee scores were not reported in one study, but range from KSS clinical of 90-91/100 (165/200) to 159/200 . 10% of knees had pain in one study. Survivorship ranged from 88-94% in 2 retrospective studies at 14 and 11 years. Revision rate

from 3 studies range from 0-7%.

Rotating Platform Devices				
Reference	Callaghan et.al.	Grodzki et. al.	Sorrells	Sorrells retro
Device Name	LCS	PFC/LCS	LCS	LCS
Knees/patients	119/86		665/521	1117/9
Age mean (range)	70	73	70	56
Deaths	18			15/18 knees
Lost to f/u	5 knees			26 knee/25 pt
Revisions/surg	0		13 (2%)	8 (6.8%)
Complications **Infection** **Aseptic loosening** **Osteolysis** **Poly wear** **Fractures** **Stiffness** **Pain** **Dislocation** **Malpositioning** **Laxity** **Sublux/subside**	 0 0 0	No information because article was in German	 4 1 2 7 6 1 1/1	 1 1 2 2 4
NSS (mean)		PFC =130 LCS =160	98% good to excellent at 11 yrs	85% good-excellent
Function score	ROM ave: 0-102^{o}			
Survivorship	100%	*	94.7%	88.1%@14yr
F/U (mean)		1 yr	1-11 yrs	8.5 yrs
Comment	Avoidance of a flexion gap thought to account for no dislocation/ osteolysis from backside wear			

* blank spaces indicate that information was not available in reference

Meniscal Bearing Devices

This consists of 5 prospective (one randomized) and 3 retrospective studies which discuss 2 devices (LCS) implanted in 1666 knees (includes bilateral) with a major diagnosis of osteoarthritis (>70%). Follow-up averaged 1-11.5 years with variable patient follow-up percentages(as low as 60%). The outcomes results are variable. Knee scores were not reported in one study, but range from KSS clinical of 70-94/100. Survivorship 93-99% in 5 retrospective studies.. Revision rate from 5 studies range from 1-9%. In the one randomized study the mobile bearing knees and fixed knees were similar.

Meniscal Bearing Devices								
Reference	Bert	Hartford	Jordan	Jordan	Kim	Minns	Muller	RosenbergHendersc
Device Name	LCS		LCS prosp	LCS Uncement	LCS/AMK	Minns Meniscal	LCS unresurfaced	LCS/PCR

							patella	
Knees/patients	43/	139/104 80 cement 50unceme 9 hybrid	160/141	473/375	120 bilat	165 RA and OA (57%)	436	35/27
Age mean (range)	63	66	68 yr OA pts	68	65	67		72
Deaths	0	37 knees	66knees	39(34 after 24 mo)	0			3
Lost to f/u		47 knees		63	4			4
Revisions/surg	4 (9.3%)	10	2(0.8%)	18(3.8%)	2/2(1.7%)	8		1 (2.9%)
Complications								
Infection		3		5				1
Aseptic loosening		7(hi in uncement 27%/31% loosening femur/tibia		2				
Fractures					1			
Dislocation	4:3-2wk,1-6mo	1		5	1	8		
Sublux/subside				4/2				
Fractures				7				
NSS (mean)	91% good-excellent			92/93	94.4/93.3	75% excellent 9%fair	NJOHS =90 @ 5yr	83 (14PTS) 60(5=Fair)
Function score					ROM =123/121	Flexion 89-103o Dec instability Dec flexion def		
Survivorship		93%	99.5%	94.6% (8yrs)	98%			97%
F/U (mean)	1 yr	7.8 yr	12 yr	2-10 (4.7)	7.4	0-5yr		?
Comment	Proper measurement of flexion gap critical to prevent dislocation of elements							

Combination of Rotating Platform and meniscal Bearing in same study

This consists of 3 prospective (none randomized) and 7 retrospective studies which discuss 6 devices implanted in 8433 knees (includes bilateral) with a major diagnosis of osteoarthritis (>70%). Follow-up averaged 20 months-13.5 years with variable patient follow-up percentages. The outcomes results are variable. Survivorship is 90-100% in at 5-10 yrs. Revision rates range to 8%.

Combination of Rotating Platform and meniscal Bearing in same study details on table Vol. 2, Appendix 3,p.240											
Reference	Buechel	Buechel /Pappas	Callaghan (8 reports)	Keblish	Keblish	Munzinger	Papchristou	Sanchez Sotelo	Steil et al	Weissinger	Thompson
Device Name	NJLCS	NJLCS	LCS/ Oxford	LCS	LCS Moveable-bearing w/ anatomic femoral groove	LCS	Oxford 9 pts Endo-model 18 pts	LCS	LCS 147 Meniscal 44 Rot Plat	LCS	LCS
Knees /patients	373/282	357: 149 cemented 208 uncement MB=140 RP= 217		963/918 (MC) 275 personal series	104/52 bilateral 1 side patella resurface 88 uncemen td 16 cement	235		101 pts	290/250	42/41	33/31
Age mean (range)	68	62	35-90	68	69	68	63-72	66	69	65.8	73
Deaths		1	42		0	0	0	0	35	1	

Lost to f/u						131 less than 2yr			99		
Revisions /surg	1	15 (4%)	65	9 (personal 3.3%)	1	8 (3%)	3 total 2 Oxford (22%) 1 endo	8 /(8%)	5 (5.4%)	0	
Infection	3	7				1	1	1			1
Aseptic loosening	3	6		4			2	1			
Osteolysis	3(1.8%)	0						2			
Poly wear				3				1			
Fractures	1	2									

Stiffness											
Pain											
Dis location	5	MB=.7% RP= 3.2%	Most common			1Patellar probs responsible for comps		2			
Sublux/ subside				4							
Fractures	1	2+ 1 trauma		2 patellar				femur			
NSS (mean)	PCR 68% excellent CRP 47%	cement 85% excellent 11.5% poor uncement 92% excellent 6% poor		Cemented LCS- 96% excellent Uncement LCS- 97% excellent	89.9 mean	95% excellent/good 4.2 yr		93			Dec pain All to 21 pain free 12 occasional

Function score								78 ave			Dec ROM
Survivorship									97.5%MB 7 yrs 100% RP		
F/U (mean)	20 yr	91mo/52 mo	5-11 yrs	2-8yr	5.24 yr			5.2yr		21 mo	20 mo
Comment					Nonresurf patella same as resurfaced patella	Acceptable results re: - degree of stability - pain relief			IM alignmt flexi/extgap balancing impt		

Unicondylar Meniscal Bearing

This consists of 12 prospective (one randomized) and 8 retrospective studies which investigates 3 devices (LCS, Oxford, Lotus) implanted in 2385 knees (includes bilateral) with a major diagnosis of osteoarthritis (>90% in all except one study). Several studies had small sample sizes (<60 pts) Follow-up averaged 2-11 years with variable patient follow-up percentages.(some less than 50%) The outcomes results are variable, 47-98% success. In one study, RA patients had better outcomes than the OA patients Survivorship 66 (6 yrs)-100% in at 5-10 yrs. Revision rates are high in several studies, reported range 0 to 30%. In this grouping, successful results were associated with specific patient inclusion and exclusion criteria, and patient anatomy.

Unicondylar Meniscal Bearing									
REF	**Device**	**Pts/Knee**	**Age**	**Revision**	**F/U**	**KSS**	**Fxn**	**Survivorship**	**Complications**
Argenson	oxford	552		45(8.2%)	14			92%	
Barrett	Oxford bicompart	62 pts RA 46% OA 54%	75	4 (7%)	4.5 yr	83% pain relief	ROM: 93-103° 93-73°		4 DVT 2 Dislocation 2 aseptic loosening 5 infxn
Bourne	Oxford Meniscal Oxford Kinematic I	67 66	67	20 (30%) 3	5.5 yr	82 88		9 deaths	15 aseptic loosening 2 patellofemoral syn 1 dislocatn 1 infexn
Carr	25 bilateral medial compartment	121/96	69	1(0.8%)	44.4 mo	75% pts no pain	ROM 95-106	99.1% @ 9yrs 1 death	Loosening displacement
Cohen	NJOHS	21/20	60	1	10 yrs	16 good-excellent		2 death	Aseptic loosening
Goodfellow	Oxford Uni Meniscal	103/85	70 OA	9 rev (9.2%)	36 mo	92% No pain		5 deaths	4 Aseptic loosening 2 Lysis 3 dislocn 2 infexn Subluxation ACL absence greater incidence of failure
Goodfellow	Oxford	125/107	67	8 rev	49 mo	89% pain free	Flexion deformity	1death	1 infxn 5disloc

w O'Conner				4 failures		free	deformity Flexion worse post op		6Aseptic loosening 2lysis
Goodfellow	Uni	25/22	67 OA, AVN,fx	1	21 mo	92% no – mild pain	Flexion worse post op		1Loosning tibia
Gunther	Oxford Uni	53/51	68	11 (21%)	5.2 yr	53% report pain w/activity		Bearing dislocation greater in lateral compartment	6 Bearing dislocation 1Plateau fracture
Harding	Oxford I, II	50/50		14 (28%)				I 66% II 86% 100% if indications met?	Poor outcome if ACL deficient
Keyes	Oxford Unicompartmental			0	5 yr	97.5% good - excellent		100%	
Kumar	Oxford Uni	100/	71	7 (7%)	11yr	Pre 62 Post 91	Pre 45 Post 71	85%	Aseptic loosening
McLardy Smith	Oxford Uni	475/	<60 >60		10yr			94% 95%	
Murray	Uni congruous mobile poly bearings	143/114	70	5 rev (3.5%)	7.6			98% 10yr	dislocations
Price	Oxford Uni	40 MIS 20 conv 40ABD TKA	57-91						
Rees	Oxford UCA	631/507 primary and failed HTO	70	19 1° (3.1%) 5 HTO				96% 10yr 66%	Uni UCA should not be used in failed HTO
Sherman	Bilateral Bicompartmental Oxford Meniscal	/32	63	5	51 mo	Pain relief in all but one	No improvements in ROM		Infection Aseptic loosening Bearing dislocation
Svard	Oxford Meniscal B uni	124/	70	6 (4.8%)	12.5			95% 10yr	Bearing dislocation
Vorlat	Oxford	41/39	62	3	5 yrs	87			Infection

	Uni								4 "other"
Weale	Oxford	31/28	70	2			Oxford scale 36.5/48		Aseptic loosening
Weale	Oxford Uni	56	80.3	2	1.4	25/28 good or excellent			
Witvoet	Lotus			18 19%	4.6	71.9% good 28% poor			Poly wear Radiolucencies Poor techniques/indications

The sponsor provides results of review articles which report on large samples grouped together and summarized with survivorship rates (section VIII) of over 2500 knees over a 5-17 years evaluation of survivorship, with a range of survival for those prosthetics of 93% to 100% over this time. The sponsor states that over 46 knees (Section XI) are available for review, however it appears that the article chosen include only two or three designs.

Review of testing shows that the amount of displacement permitted in the anterior-posterior and medial and lateral directions is highly variable

Meta analysis (Vol. 1 Section VIII p. 68, Vol2, Appendix 4, p.272) [see statisticians review, "problems" and analysis below]

The sponsor presents the result of a meta analysis of 21 studies reporting the outcome of 22 cohorts which enrolled a total of 2,490 patients (2,870 knees).The mean enrollment per study was 138, greater than 10 patients per study was allowed however. Mean follow-up was 6 years for these patients, The mean age for these patient was 66 years with a slight majority of women(62.3%), The majority of patients had Osteoarthritis (82%) and 13% were bilaterally implanted. The outcome of the meta analysis was compared to a review of over 9000 patients with fixed bearing knees reported by Callahan, et al.

This table was provided as a summary. The rate of revision was higher in the mobile bearing knees at 6.4% vs. 3.8% for fixed bearing knees. Two particular mobile bearing knees have a high rate of revision (30%): the oxford phase I and the Accord TKA, which are both, according to the sponsor no longer used. The mean percentage of patients with good or excellent outcomes following mobile bearing knees replacement is 90.3% which was similar to the percentage reported in Callahan's review (89.3%) and lower than the fixed bearing group when comparing improvement in a global rating scale outcomes. 91% vs. 100%. "The range of the percentage of patients with good or excellent outcomes following mobile bearing knee replacement was 35% to 100%." Vol.2 Appendix 4, p. 277.

Meta analysis results :Comparison of mobile bearing knees vs. fixed bearing knees (Vol. 1 Section VII, p.68)			
	Mobile bearing knees outcome result	Mobile bearing knees outcome result excluding Oxford phase I and Accord knee	Tricompartmental Fixed bearing knee outcome result (Callahan et.al.)
# knees	2870	2729	9879
Weighted mean yrs of f/u	6.0	6.4	4.1
# cohorts analyzed	22	20	154
Weighted mean%	90.3	93.4	89.3

good/exc ellent			
% improvement in global rating scale	91.4	91.4	100
Weighted mean postoperative global rating scale score	87.8	89	86.6
Weighted mean % knees with any revision	**6.4**	**5.1***	**3.8**

*The revision rate described in these studies is 30%.

The sponsor provided a survival meta-analysis which compared mobile bearing knees to fixed bearing knees based on survival estimates and reports reviewed by Callahan. Estimates of implant survival were extracted from 37 articles (1989-2002) Implants were grouped into categories: 21 were mobile bearing knees and 16 were fixed bearing. From these 111 survival estimates were extracted: 40 mobile bearing knees and 71 fixed bearing. The survival rates were "reduced" by the sponsor, when multiple survival estimates were provided for a unique device, data was reduced retaining the estimate with the most consistent definition of "revision" and the longest length of follow-up.

Mobile bearing knees and Fixed bearing implant survival compared			
	Overall survival	Mobile bearing knees	Fixed Bearing Knees
Mean follow-up	12-17 years	12.5 yrs	17.2 yrs
WLS estimate	0.9198	0.9263	0.9133

Survival meta analysis

There were 21 articles which summarized survival for devices which were grouped into a mobile bearing category and 16 grouped into a fixed bearing category. From these a total of 111 survival estimates were extracted, with 40 mobile bearing device group estimates, and 71 fixed bearing device group estimates. For each implant, information on the average period of follow-up and the total number of knee implants was tabulated.

There are several problems with the performance of this meta-analysis**:**
Judgments were made as to which survival reports to include "Since the number of survival estimates appearing in a given publication ranged from 1 to 30, data was reduced allowing only one estimate for each unique device (or set of similar devices within the mobile or fixed bearing group) from each article. When multiple survival estimates were provided for a unique device, data was reduced retaining the estimate with the most consistent definition of revision and the longest length of follow-up."
Reporting style was also problematic. Authors reported data using the patient or knee as the unit of analysis. The number of "cases" or number of knees was used for this meta analysis. The data abstraction was completed by a research professional who was educated in the data abstraction requirements. Only variables that were consistently reported across the majority of studies could be analyzed. Difficulties in abstracting data resulted from two types of missing data. The first came when authors did not mention a variable of interest in a study. The data abstractor could not determine if the variable was absent from the study or if it was not reported. The second difficulty arose when the variable of interest was mentioned as part of a subset of enrolled patients, but were not mentioned in number or stratified in the results.

The second problem involved the author's choice of global knee-rating system and the method of reporting used for the scores. To allow comparison across studies, the mean preoperative and postoperative global knee-rating scale score using a 100-point scale was used.
The reporting of complications also showed variability. To allow comparison across studies, perioperative complication data were not collected. Complication data that was collected included the following categories: knees with any complication, knees with any revision, knees with revision for mechanical failure, knees with revision for aseptic loosening, and knees with revision for septic loosening. The anatomic portion of this classification scheme

identified the prostheses by treatment of the posterior cruciate ligament (sparing, sacrificing, or both sparing/sacrificing of PCL used in same study). When an article reported across more than one anatomic classification and provided patient characteristics for each group, the data were treated as two separate articles. When an article reported data across more than one classification but did not provide patient characteristics for each group, the study was considered as a mixed group of prostheses.

The sponsor does a meta analysis of the new device class based on studies with greater than 15 patients enrolled per study reporting on this device, (randomized, non randomized and uncontrolled series, single investigator, multicenter are all reported in one large group). They then use these results and compare it to another meta analysis already completed on another class of devices in which studies were included if 15 patients were enrolled and outcomes were measured by a global out come scale (not necessarily all the same scale within and between the studies) Then the sponsor took the two meta analyses and compared the mean numbers for follow-up, revision, device survivorship and good to excellent results, without defining what patient inclusion/exclusion criteria were, what the criteria for revision are and what scales were used to rate good to excellent out come in a global scale.

For a meta-analysis, all the demographic and study design, assessment issues also have to be considered and it does not appear that these are completed for both analyses The conclusion is that the device classes have the same outcomes. However, the sponsor only provided 3 actual randomized studies in which a representative device from each class were compared prospectively under controlled conditions, and the meta analysis was not properly performed. Nonetheless the number of patients implanted is large and the results varied, the summary may be misleading by providing one mean for all devices. This may be better characterized by summarizing subgroup results.

Risk to Health

Risks may be identified from:

1. The proposed and final classification rules (based on the Classification Panel's recommendation)
2. Review of the literature
3. Review of the MDR's
4. Labeling for the device

MDR (Volume 1, section IX)

A search of the MDR reports found 385 MDR, 365 were of one manufacturer.
Injuries: 333
Malfunctions: 29
Death : 1
Other: 2
This table was constructed from the sponsor's data listing in summary by type

Type of event	LCS Posterior Stabilized	LCS Rotating Platform	LCS Meniscal Bearing	LCS Unknown type	LCS Femoral	LCS Tibial	LCS Patella
Loosening	3	18		1	3	4	2
Metal/poly separation							25
Bearing Fracture		3	35	4			2
Effusion	10	1		1			1
Incorrect bearing		1					
Physician error					1		
Impingement and Swelling	4						
Infection	2				1		1
Unknown	2	1	1	1			1
Pain and Swelling	46			2			
Broken Post	1						

Patella spin out							2
Poly wear		11	11				3
Revision	1						
Painful ROM	1						
Poly defect	3						
Subluxation			1				
Bearing Failure		2	11				1
Patella locked							1
Impingement/wear	1	2					
Fractured meniscal bearing			2				
Loosening with debris		1					
Fractured Poly		1				1	5
Allergic Reaction				2			
Pain	15	1	1		2	2	
Failed tibia	1						1
Pain/inflammation	1						
Catastrophic Poly failure			1				
Pain bilateral revisions	5						
Bearing dislocations		5			1		
Bleeding patella							1
Patella/(avulsion) fracture	1						4
Stiffness ROM	2						
Bearings disintegrated			1				
Metallosis			1				
Porocoat separation					1		
Bent bearing track						2	
Poly crumbled		1					
Knee prosthesis failure		1	2	1			3
Package defect					1		
Poly pitted				1			
Implant defect							2
Mislabeled	1		3	1			
Malpositioned		1					
Implant did not fit			1				
Unknown revision						1	1

Although the sponsor provides a list of the MDRs of the one device that is marketed in the US, similar information is not available for mobile bearing knees devices in use outside the US. Although literature articles provide some information, many do not report a complete profile of the adverse events.

Risks associated with knee surgery include infection, Pulmonary embolism, gastrointestinal and genitourinary problems. Those associated with the device are listed above. Risks were grouped into 3 general categories:

?? Infection

?? Adverse tissue reaction
?? loss or reduction of joint function/revision

The sponsor provided two tables which evaluated patient risk using the engineering tool, "Failure Modes and Effects Analysis" (FMEA).(Volume 1, Section X, pp. 85-93) The first table, contains the hazards common to both fixed and mobile bearing knees while the second contains the additional hazards specific to mobile bearing knees, exclusively. Potential hazards are listed within each category, as applicable. Potential effects from those hazards and an initial risk assessment are presented.

Each hazard in these tables has provided one or more solutions or actions designed to reduce the potential risk to the patient. An assessment of the final risk after those solutions/actions are implemented is presented. In addition, special controls are identified for each of the hazards.

However, because the mechanics and designs are significantly different , the testing demonstrated the safe use of fixed bearing knees may not be applicable to the mobile bearing designs.

The sponsor contends that many of the identified risks can be mitigated by material standards, proper device design, labeling and by controlling the device quality through Good Manufacturing Practices (GMP) Quality System Regulations (QSR). Numerous FDA guidance documents, ISO standards, and ASTM standards are available to provide specific guidance regarding materials, testing and labeling.

There are two risks that the sponsor believes are unique to mobile bearing knees and not common with fixed bearing knees. These are: the potential for the mobile bearing to rotate beyond design objectives, and the potential for greater wear due to an additional articulating surface are hazards related to the design of mobile bearing knees. For these two risks, there are no recognized standard testing methods to predict the modes of failure associated with these risks.

The sponsor also provides the following in support of the reclassification: (Volume 1, Section X)

- a review of the requirement for various types of special controls, including a complete listing of FDA guidance documents, ISO Standards, and ASTM Standards that apply to knee prostheses.
- A breakout of guidance documents and standards, assigning each to one of the three general categories of risk (infection, adverse tissue reaction, and loss or reduction of joint function).
- Proposed Labeling for mobile bearing knees: a listing of indications, contraindications, warnings, and adverse events relevant to mobile bearing knees, including total knees and unicondylar knees.
  Also, included is proposed package insert content that includes information on total and unicondylar knees.
- Tests and test methods suggested for mobile bearing knees.

In the summary of risks a sponsor is charged with the task of providing a summary of the following information:

1. The incidence rate
2. Cause
3. Sequelae of the risk
4. Information demonstrating that the stated risk is not a potential hazard of the device, if available.

Wear is defined through various bench studies, in-vivo explants are not presented and the results of bench testing is compared to hip wear data not knee data. There are studies which review explants and there are several studies which characterize poly wear in fixed bearing knees which should be included. The biomechanical characteristics are summarized in the preclinical review.

Known Potential Benefits

The potential benefits of the device include decreased pain and improved function; however it is not yet proven that these devices are better or even completely equivalent to a well functioning fixed bearing knee. There are few published randomized controlled studies which examine the outcomes and risks of the fixed and mobile bearing knees side by side. In some other reports, the survival rate of mobile bearing knees are slightly lower than fixed bearing

knees, the patients are not more active and the revision rate slightly higher, showing that prevention of mechanical failure is not higher. The theoretical advantage of a longer device life in younger, active patients is not proven as most studies the patients have a mean age of 65 or greater. There are some studies which have shown that the contact stresses of fixed bearing knees may be equivalent to those of mobile bearing knees and few explant studies have validated that reduced wear actually occurs in situ in each type. Osteolysis similarly has not been shown to be different in the mobile bearing knees designs. (AAOS instructional course lectures: Callahan, C. Mobile Bearing Knees: Concepts and Results, 2001.)

That having been said, the sponsor does provide multiple retrospective and non randomized studies which report good to excellent clinical results for the majority of study patients.

Labeling: (Section X)
Indications
The data may not support indications for steroid dependent RA or valgus, varus and flexion deformities. Instability of the knee in general should be excluded. There is no information to assist a physician to choose a Mobile bearing knees over a fixed bearing prosthesis, particularly in the indications statement, as this has not been properly studied For the unicondylar knee indication should be correctable varus and valgus deformities is misleading. This should be further clarified that both should not be present

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The memo that follows summarizes the submission and the responses to FDA's deficiencies from a clinical perspective.

Summary
This reclassification presents data to support the petition for reclassification of all mobile bearing unicondylar, bicondylar condylar and tricompartmental knees from Class III to Class II. This includes clinical data from IDE and outcome studies, peer reviewed journal articles and meta- analysis comparison analyses between fixed and mobile bearing systems related to adverse events and effectiveness outcomes. The sponsor believes that this information provides strong evidence of the safety and efficacy of mobile bearing knees, and that the risks associated with these devices are not adequately defined. Before a decision can be made whether reclassification from Class III (Premarket Approval Application) to Class II (Special Controls) is justified, further information and clarification is needed. The sponsor provides responses to the requests for further information as requested in the FDA letter dated February 2004.

Responses to deficiencies:
1a. The sponsor provided Appendix 1a with multiple articles on wear, including back side wear not present in the original petition. It includes a synopsis of articles on wear defined by these articles.
Review: This response is adequate and the sponsor provides an adequate review of current literature. It serves to corroborate the premises that:

- **there are wear issues for both FBK and MBKs which may lead to osteolysis associated with loosening and wear debris**
- **Wear generated by a total knee prosthesis is dependent on the conformity of the components with each other, the type of polyethylene used, the patient implanted, and the relative motion that occurs at the interface between the components**
- **The variety of the amount and type of motion at the component interfaces is as varied as the types of prosthetic designs.**
- **Back side wear which occurs with any type of knee prosthetic to varying degrees. Studies to detect this risk are few, fraught with difficulty and have not been definitive about how to assess this risk fully.**

Deficiency 1.b&c.
The sponsor has filled out the table FDA presented as requested to facilitate review of this reclassification petition. It states the **representative mobile bearing knees, the biomechanical advantages and disadvantages,**

survivorship[(survivorship for each mobile bearing knee device type was calculated by averaging the survival estimate and mean follow-up reported in the article. Each article included had a minimum follow-up period of 5 years. If multiple definitions of survival were included, the most conservative definition was used.) With the exclusion of this poor performer (Thackeray,UK), all mobile bearing device groups report >90% survivorship (note: some of the groups have a small sample size).]

Response continued: **Risks and special controls** [OSMA divided them into two groups:

1- risks and special controls that are common to fixed and mobile bearing knees, and for which there are no special issues related to mobile bearing design features.

Categories: sterility, biocompatibility, metal sensitivity, metal corrosion and separation of the porous coating from the metal substrate. These generic risks and related special controls were discussed in the original petition and were not included in Table 1.c. This is adequate as the sponsor has already provided these previously

Risks and special controls includes those that have unique considerations when applied to mobile bearing knees when compared to the same special control applied to fixed bearing knees. For example, wear testing of mobile bearing knees needs to account for additional articulating surface wear and for rotational movement. Section Appendix 1.c. also includes a section entitled "Special Controls with Unique Mobile bearing knees Considerations". This text provides descriptions of each special control, with an explanation of how the control will provide reasonable assurance of safety and effectiveness. In addition, the applicable FDA guidance, ASTM and/or ISO documents are listed for each special control. Where no standard test method has been defined, OSMA has recommended a test method.

Test	**Rationale**	**Current Standard**	**Suggested**
Wear Test	-Simulate sliding Rolling and rotational mvmts	ASTM 1715 ISO 14243	
	- address backside wear	In vitro simulator/gravimetric analysis	Volume of wear scar Observed changes to engraving marks
Particulate analysis	Determine risk of Osteolysis due to particulate	ASTM F-2025 ISO 14243-2	
Spin Out test		None	ASTM F-1223
Tibial Tray Fatigue Test		ASTM F-1800 ISO 14879-1	
Dissociation /Binding Test		None	Component interlock Strength Testing SC guidance PF & FT M/P porous coated Uncemented Prosthesis
Overhang Deformation Test		none	ASTM F-1715 ISO 14243-1
Contact Area/ StressEvaluation (load damage)		None	Contact Area guidance Semi Constrained knees ASTM F-1715 ISO 14243
PatelloFemoral		None	Lateral stability of

Lateral Stability test			the PF joint testing
PE Metal shear Fatigue and static Tensile strength test			Static Tensile Pull-off and shear Fatigue Testing ASTM F-1672
Patello Femoral Contact Stress(load Damage and Patellar wear		None	ASTM F-1715 ISO 14243-1
Wear test of stop		None	ASTM 1715 ISO 14243-1
Labeling, Surgical Technique surgeon training		None	21 CFR 801,820 and ISO 6018

d. The sponsor provides Table 1.d. (see Appendix 1.d.) which provides a summary comparing the various mobile bearing knee device groups with fixed bearing devices. And Supplement 1.d., which lists the clinical outcome details of each study that was utilized to provide the data in table 1.d.

~~Review~~: The sponsor has provided the information as requested, however because the sample size is small no statistical conclusions can be reached. It is note worthy that only few mobile bearing knee designs are approved in the US and those are the subject of the reclassification petition.

This table overstates the revision rate of Fixed Bearing Knees. In the recent NIH consensus the overall prosthesis failure rate is given as 1% per year or 10% at 10 years. It is worth noting that the revision rate of mobile bearing knees is not less than that of fixed bearing devices.